

Domperidone: an indication of how many sudden deaths in France could be prevented by avoiding this low-efficacy drug

Abstract

- **Domperidone is a “hidden” neuroleptic that has been used since the 1980s to treat common nausea and vomiting and similar symptoms, with modest efficacy. It prolongs the QT interval on ECG and exposes patients to the risk of cardiac arrhythmias. Case-control studies have shown that sudden cardiac death is about 1.6 to 3.7 times more frequent with domperidone exposure.**

- **Data from the “General Sample of Beneficiaries” of France’s mandatory health insurance system show that, in 2012, domperidone was dispensed at least once to about 7% of the country’s adult population, i.e. to about 3 million adults. Another drug known to potentially increase the risk of arrhythmia associated with domperidone was co-dispensed on the same day to about 23% of these patients.**

- **In France, given the incidence of sudden death, a prudent assumption makes it plausible that domperidone caused about 25 to 120 premature deaths in 2012.**

- **In practice, domperidone can easily be replaced with solutions that are better for patients.**

As its international nonproprietary name (INN) indicates, *domperidone* is related to various neuroleptics, such as *risperidone* (1,2,3). It has been used since the early 1980s, not as a psychotropic drug, but to alleviate nausea and vomiting and various common gastrointestinal disorders: hence it is a “hidden” neuroleptic (4,5).

In 1986, the injectable form of *domperidone* was withdrawn from the market due to the cardiac arrhythmias and deaths it caused. The oral forms remain on the market (4).

In 2004, the French Pharmacoeconomic Committee (*Commission de la Transparence*) reviewed the therapeutic value of *domperidone*, using data from a European referral procedure that had been conducted in order to harmonise the summaries of product characteristics (SPCs) for *domperidone*-containing drugs across the European Community. Without mentioning cardiac harms, it rated *domperidone*’s therapeutic value “insufficient”, except in the relief of nausea and vomiting, for which it was rated “moderate” (a)(6).

Since 2005, it has been established that *domperidone* prolongs the QT interval on ECG, as do the other neuroleptics, and Dutch and Canadian case-control studies have shown an increased incidence of sudden cardiac death in adults exposed to *domperidone* (b)(3,7,8,9,10). According to these studies, the incidence was about 1.6-fold to 3.7-fold higher in patients taking *domperidone*. The risk appeared even higher for patients taking more than 30 mg of *domperidone* a day, while the SPC authorises a maximum daily dose of 80 mg.

How many patients in France are exposed to *domperidone* and the associated risk of sudden death?

About 8% of the French population exposed each year

The French Health Data Institute (IDS) allowed *Prescrire* to study *domperidone* exposure using the “General Sample of Health Insurance Beneficiaries” (EGB), established and regularly updated by the French National Health Insurance Fund for Salaried Workers (CNAMTS) to represent 1/97th of the population covered by France’s mandatory health insurance system. Patient and prescriber data are anonymised in the EGB. Drug exposure data are obtained from prescriptions presented for reimburse-

ment after the drugs have been dispensed at a community pharmacy (11).

About 3 million adults exposed annually. In 2012, *domperidone* was dispensed at least once for 49 354 patients in the EGB, i.e. 7.7% on average (up to 18% in children 0 to 4 years old) (12).

The 2 Dutch studies that showed an increased risk of sudden death with *domperidone* excluded children and cancer patients (7,9). We aimed to determine the *domperidone* exposure of this population in France, i.e. adults without cancer. In 2012, among the adults in the EGB who were not flagged as having cancer as a long-term illness, we identified 31 190 (6.4%) to whom *domperidone* had been dispensed at least once. Scaled up to the entire insured population of France, that would correspond to about 3 million adults (12). *Domperidone* had been dispensed at least once to 11.8% of adults flagged as having cancer as a long-term illness.

This level of exposure has remained more or less constant for years. The EGB data suggest that between 2003 and 2013, *domperidone* was dispensed at least once to about 27 million people in France (12). The numbers exposed to the drug fell by only about 6% between 2011 and 2012.

Often one box during the year. In 2012, adults without cancer in the EGB to whom *domperidone* was dispensed at least once received 1.6 boxes on average (12). About 80% received one box only. In most cases they were boxes of 40 tablets, usually of the 10-mg strength, although one-fifth contained the 20-mg strength.

The data in the EGB do not specify the daily dose prescribed. The French Pharmacoeconomic Committee reported in 2007 that the average daily dose prescribed for adults was ►►

► 31 mg for the 10-mg strength, and 54 mg for the 20-mg strength, corresponding to 2 weeks' treatment for one box of 40 10-mg or 20 mg tablets (13).

Prolongation of the QT interval is detectable from the third day of *domperidone* treatment, and the authors of the Canadian study reported that sudden death was more frequent the first time the drug was dispensed than with subsequent prescriptions (no quantitative data provided) (10,14). The plasma elimination half-life of *domperidone* is generally about 7 to 9 hours, and longer for patients with renal impairment (5).

Very frequent interactions, increasing cardiac risks. In 2012, about 22.8% of the adults in the EGB who were not flagged as having cancer and who received *domperidone* were also given, on the same day, at least one drug known to increase the risk of torsades de pointes, either by further increasing the risk of QT interval prolongation, or by slowing the heart rate, inducing hypokalaemia, or increasing the plasma concentration of *domperidone* through inhibition of cytochrome P450 3A4 (12,15,16).

For example, *domperidone* was co-dispensed on the same day as another neuroleptic for 2.9% of this population, while 4.3% were co-dispensed a drug that inhibits cytochrome P450 3A4 (12).

An indication of the number of sudden deaths in France

Sudden cardiac deaths are not reported in the EGB. But EGB data can be used to estimate the number of sudden deaths caused by *domperidone*.

The estimated incidence of sudden cardiac death in Europe is generally reported to be between 50 and 100 per 100 000 population per year, depending on the study (7,17-19). A study published in 2013, as an abstract, showed an incidence of about 29 per 100 000 for the Paris region, with a 7% survival rate (20).

Probably about 25 to 120 deaths in 2012 in France. If we take these recent French data into account, the fact that each patient exposed to *domperidone* takes it for about 2 weeks, and that the incidence of sudden death is about 60% higher during exposure to *domperidone* (as reported in the Canadian study), we estimate that *domperi-*

done caused about 25 deaths in France in 2012. This figure would be about 120 if we assume an approximately 3.7-fold increased incidence during exposure to *domperidone* (as reported in the Dutch studies). It would be even higher if the incidence of sudden cardiac death is greater than 29 per 100 000, as reported in other European studies.

Possible sources of over- and under-estimation. These numbers may be overestimated, notably because some patients do not take or complete prescribed treatments. However, the same limitation applies to the Dutch and Canadian studies that showed the increased risk with *domperidone*.

These numbers are probably underestimated, because the increase in the incidence of sudden death appears even greater in patients taking more than 30 mg of *domperidone* daily, which is very easily done with the 20-mg strength.

Additional deaths would have occurred in cancer patients. In the EGB, adults flagged as having cancer were twice as likely to be exposed to *domperidone* as the others (12).

Additional deaths would have occurred in hospitalised patients. One study showed that, in this population, *domperidone* therapy increases the incidence of cardiac arrest about 5-fold (8).

Child deaths may also have occurred, since in 2012, *domperidone* was dispensed for 18% of children aged 4 years or less, corresponding to about 680 000 children in total; but sudden cardiac death is much rarer in children than in adults (18).

Regulators too slow to act to protect patients

The first two Dutch studies were published in 2005 and 2006 (7,8). Prolongation of the QT interval was added discreetly to the French SPC in 2004, and the risk of arrhythmia was added in 2008 (3,21).

In late 2011, the French Health Products Agency warned health professionals about the risk of sudden death, and a letter to doctors and pharmacists from Janssen-Cilag, the pharmaceutical company that markets Motilium®, mentioned the studies published in 2010 (funded by Johnson & Johnson, to which Janssen-Cilag belongs) (9,10,21).

In late 2013, the French Agency summarised the review of *domperidone*-containing medicines that the European Pharmacovigilance Risk Assessment Committee (PRAC) began in March 2013, thus (our translation): "(...) *the cardiac risk profile has been confirmed. In order to enable appropriate risk minimisation measures to be put in place, particularly as regards the optimal dosage and treatment duration and the measures to take concerning the various pack sizes available within the EU, an additional list of questions has been drawn up*" (22). The PRAC's recommendation is due in March 2014 (22).

In practice: provide better patient care without domperidone

The modest symptomatic "efficacy" of *domperidone* does not justify the associated risk of premature death.

This has been known for years. In France, the warning issued by the Agency and one drug company in late 2011 has resulted in only a marginal decrease in exposure, and about 3 million adults were exposed to *domperidone* the following year.

In practice, the disorders for which *domperidone* is prescribed are often self-limiting or resolve with simple dietary measures (23). For patients who nevertheless want drug therapy, one option is a truly harm-free placebo. For symptoms caused by gastroesophageal reflux disease, a proton pump inhibitor such as *omeprazole* is preferable to *domperidone*. And in the rare situations in which a gastric "motility modifier" appears justified, *metoclopramide* can be considered, but with great caution: at the lowest effective dose, monitoring very closely for its adverse effects, given that this drug is also a "hidden" neuroleptic. *Metopimazine* or *alizapride*, another couple of "hidden" neuroleptics, are best avoided, as they offer no demonstrated advantages over *metoclopramide*.

As of 2014, there is no reason for *domperidone* to be used, paid for by health insurance systems, or left on the market. There are better solutions for patients.

©Prescrire



.....

► **a-** Evaluation data were also examined and left out of the SPC, due to lack of evidence of superiority over placebo in the following situations: migraine; travel sickness; gastroesophageal reflux disease; nausea and vomiting induced by chemotherapy or dopamine agonists used to treat Parkinson's disease; and postoperative nausea and vomiting. Over 2000 patients were included in these studies (ref 6). In nausea and vomiting domperidone has not been shown to be more effective than metoclopramide. As of early 2014, according to the French SPC, domperidone is authorised for use in children and adults in nausea and vomiting and, in adults only, for "epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents" (ref 5).

b- The definition of sudden cardiac death varies between studies. It usually means unexpected death in a person who was observed in a stable medical condition less than 24 hours previously, with no evidence of a non-cardiac cause (such as suicide or stroke, etc.). With immediate medical care, a small percentage of patients survive sudden cardiac arrest (ref 9,10,18,20).

.....

.....

Selected references from Prescrire's literature search.

- 1- Prescrire Editorial Staff "Common stem-peridone" *Prescrire Int* 2012; **21** (131): 235.
- 2- Prescrire Rédaction "6-1. Patients ayant un reflux gastro-œsophagien" *Rev Prescrire* 2013; **33** (362, suppl Interactions médicamenteuses).
- 3- Prescrire Rédaction "19-1. Patients psychotiques" *Rev Prescrire* 2013; **33** (362, suppl Interactions médicamenteuses).
- 4- Prescrire Rédaction "Domperidone: troubles cardiaques ajoutés dans les RCP de ce neuroleptique" *Rev Prescrire* 2009; **29** (313): 821.
- 5- ANSM "Motilium 10 mg. Résumé des caractéristiques du produit" 30 July 2013. <http://agence-prd.ansm.sante.fr> accessed 3 February 2014: 9 pages.
- 6- Commission de la transparence "Avis de la Commission - Biperidys 20 mg" 30 June 2004: 13 pages.
- 7- Straus SMJM et al. "Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death" *Eur Heart J* 2005; **26**: 2007-2012.
- 8- De Bruin ML et al. "In-hospital cardiac arrest is associated with these of non-antiarrhythmic QTc-prolonging drugs" *Br J Clin Pharmacol* 2006; **63** (2): 216-223.
- 9- Van Noord C et al. "Domperidone and ventricular arrhythmia or sudden cardiac death" *Drug Saf* 2010; **33** (11): 1003-1014.
- 10- Johannes CB et al. "Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study" *Pharmacoepidemiol Drug Saf* 2010; **19**: 881-888.
- 11- De Roquefeuil L et al. "L'Échantillon généraliste de bénéficiaires: représentativité, portée et limites" *Points de repère* 2009; (25): 12 pages.
- 12- Prescrire Rédaction "Domperidone et EGB": 15 pages.
- 13- Haute autorité de santé - Commission de la transparence "Avis de la Commission-Peridys" 12 September 2007: 2 pages.
- 14- Prescrire Editorial Staff "Domperidone: QT prolongation in infants" *Prescrire Int* 2010; **20** (112): 14.
- 15- Prescrire Rédaction "Fiche E2d: torsades de pointes médicamenteuses en bref" *Rev Prescrire* 2013; **33** (362, suppl Interactions médicamenteuses).
- 16- Prescrire Rédaction "Fiche P1a: inhibiteurs et substrats de l'isoenzyme CYP 3A4 du cytochrome P450" *Rev Prescrire* 2013; **33** (362, suppl Interactions médicamenteuses).
- 17- de Vreede-Swagemakers JJM et al. "Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival" *J Am Coll Cardiol* 1997; **30** (6): 1500-1505.
- 18- Byrne R et al. "Multiple source surveillance incidence and aetiology of out-of-hospital sudden cardiac death in a rural population in the West of Ireland" *Eur Heart J* 2008; **29**: 1418-1423.
- 19- Deo R and Albert CM "Epidemiology and genetics of sudden cardiac death" *Circulation* 2012; **125**: 620-637.
- 20- Bougouin W et al. "Incidence, characteristics and outcome of sudden cardiac death in France" *Eur Heart J* 2013; **34** (suppl 1): 328.
- 21- ANSM "Médicaments à base de domperidone et sécurité d'emploi cardiovasculaire - Lettre aux professionnels de santé" 6 December 2011. www.ansm.sante.fr accessed 26 January 2014: 3 pages.
- 22- ANSM "Médicaments contenant de la diacé réine et de la domperidone, médicaments à base d'octocog alpha et de zolpidem, vaccins anti-HPV - Retour d'information sur le PRAC" 6 December 2013. www.ansm.sante.fr accessed 26 January 2014: 3 pages.
- 23- Prescrire Rédaction "Patientes enceintes gênées par des nausées-vomissements modérés" *Rev Prescrire* 2013; **33** (358): 594-600.